Structural basis for HIV-1 DNA integration in the human genome

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Integration of the human immunodeficiency virus type 1 (HIV-1) cDNA into the human genome is catalyzed by the viral integrase protein that requires the lens epithelium-derived growth factor (LEDGF), a cellular transcriptional coactivator. In the presence of LEDGF, integrase forms a stable complex *in vitro* and importantly becomes soluble by contrast with integrase alone which aggregates and precipitates. Using cryo-electron microscopy (EM) and single-particle reconstruction, we obtained three-dimensional structures of the wild type full length integrase-LEDGF complex with and without DNA [1]. The stoichiometry of the complex was found to be $(integrase)_4$-$(LEDGF)_2$ by mass spectrometry analysis and existing atomic structures were unambiguous positioned in the EM map. *In vitro* functional assays reveal that LEDGF increases integrase activity likely in maintaining a stable and functional integrase structure. DNA-Protein cross-linking experiments show specific interaction between viral DNA and the C-terminal domain of integrase. Upon DNA binding, IN undergoes large conformational changes. Cryo-EM structure underlines the path of viral and target DNA and a model for DNA integration in human DNA is proposed (see fig. 1, overleaf).

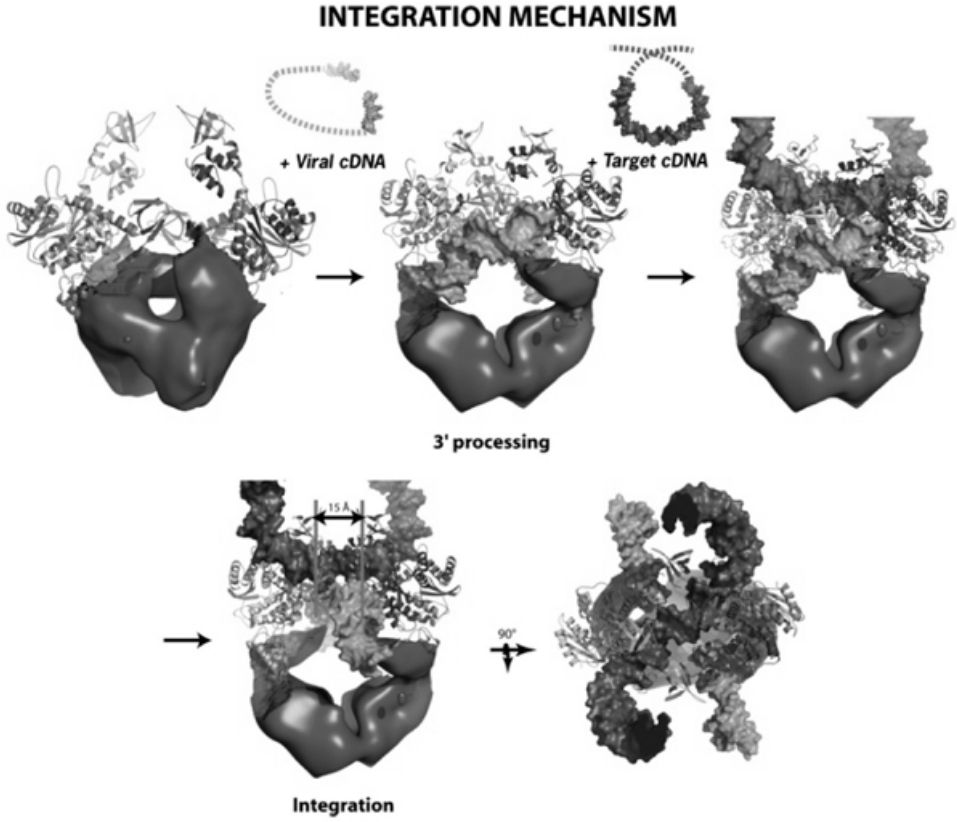

Figure 1
Proposed mechanism for thei ntegration of viral cDNA into the host genome: The LEDGF envelope is represented in blue; the integrase tetramer is shown as atomic structures. The viral DNA is in orange and the target DNA in red. On target DNA binding, there is a conformational change of the integrase proteins to position the viral DNA for the integration within 5 bases pairs in the target DNA.

References

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